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High sensitivity C-reactive protein is associated with the metabolic syndrome independent to viral and bacterial pathogen burden

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ABSTRACT

Aim: To investigate the influences of bacterial or viral pathogen burden in the relationship of high sensitivity C-reactive protein (hs-CRP) and the metabolic syndrome in a population-based study.

Methods: Data from 1754 men and women aged ≥25 years, from the Persian Gulf Healthy Heart Study were analyzed. The definition of the metabolic syndrome according to the Adult Treatment Panel III was used. Sera were analyzed for IgG antibodies to *Chlamydia pneumoniae*, Herpes simplex virus type 1, *Helicobacter pylori* and cytomegalovirus using ELISA. Measurement of CRP by a high-sensitivity CRP assay was done.

Results: The subjects with the metabolic syndrome had a higher geometric mean of CRP levels than the normal persons ($p < 0.0001$). A linear relationship between an increase in the number of metabolic syndrome components and CRP concentrations was observed (p for trend < 0.0001). In multiple logistic regression models, hs-CRP showed significant associations with the metabolic syndrome after controlling for cardiovascular risk factors and infectious burden divided into 2, 3 and 4 pathogens [OR = 2.06, CI (1.32–3.21), $p = 0.001$; OR = 1.75, CI (1.26–2.42), $p = 0.001$; OR = 2.12, CI (1.46–3.08), $p < 0.0001$; respectively].

Conclusion: There was a strong association between inflammation and the metabolic syndrome independent to viral and bacterial infectious burden.

1. Introduction

Metabolic syndrome means a clustering of anthropometric, physiologic, and biochemical abnormalities, it is a significant contributor to cardiovascular morbidity and mortality [1–3]. The National Cholesterol Education Program (NCEP) Adult Treatment Panel III introduced a definition to identify individual with high risk for cardiovascular disease and/or type 2 diabetes [4].

The role of inflammation in the development of insulin resistance, the metabolic syndrome and all stages of the atherosclerosis was investigated [5–8]. There is growing evidence to suggest chronic, low-grade and subclinical internal inflammation in the etiopathogenesis of the metabolic syndrome [9]. Measurement of the concentration of C-reactive protein (CRP), an acute phase reactant, has been used in the diagnosis and monitoring of chronic, low-grade

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inflammation. It is produced by the liver under induction by IL-6 and TNF-alpha [10].

In epidemiological studies, an increased level of CRP has been associated with the metabolic syndrome and its components, among children, youth and adults [11–17]. Some prospective epidemiological evidence linking inflammation with the metabolic syndrome has been accumulated [18–20].

Based on these evidences, some investigators have suggested that hs-CRP should be added in the definition of the metabolic syndrome and for the creation of an hs-CRP modified coronary heart disease risk score useful for global risk prediction in both men and women [21–22].

From another view, viral and bacterial infections induce production of various cytokines and can amplify inflammatory mediators, resulting in insulin resistance, the central pathological mechanism of the metabolic syndrome [23]. Therefore, it has been suggested that inflammation is behind the link between pathogen burden and insulin resistance [24]. In fact, there are limited studies about the association of chronic subclinical infections and the development of chronic insulin resistance and the metabolic syndrome or its components [24–27].

Recently, we have shown that the metabolic syndrome, which occurs very frequently in our general population, had a significant association with prior infection with *Chlamydia pneumoniae*, *Helicobacter pylori*, cytomegalovirus and herpes simplex virus type 1 [27]. However, whether the presence of chronic subclinical infections with bacterial or viral pathogens influences the relationship between hs-CRP and the metabolic syndrome has not been well established yet.

We therefore investigated association of the metabolic syndrome and increased level of hs-CRP, regarding pathogen burden, in a large-scale, community-based study in an Iranian population.

2. Materials and methods

2.1. Community sampling and baseline examinations

We conducted the present study as part of the Persian Gulf Healthy Heart Study, which was a prospective population-based cohort study based on men and women subjects aged ≥25 years, started in 2003–2004. The Persian Gulf Healthy Heart Study was designed to determine the risk factors for cardiovascular diseases among the northern Persian Gulf population (Bushehr and Hormozghan Provinces) and to develop community-based interventional projects to change the lifestyles of the population and to present the rising threat of cardiovascular diseases in the region. The design of this study encompasses two major components: phase I is a cross-sectional prevalence study of unhealthy lifestyle and ischemic heart disease and associated risk factors, and phase II is a multiple interventional project for reduction of cardiovascular diseases in the region.

Detailed information about the methods and procedures of this study is available elsewhere [28]. In an ancillary study to the Persian Gulf Healthy Heart Study, a total of 1754 (49.2% males, 50.8% females) subjects were selected through a stratified multistage design from major ports of Bushehr Province (an Iranian province with the greatest boarder with the Persian Gulf).

All subjects were asked to fast and to present to the survey center between 7.30 and 9.30 a.m. Blood pressure was assessed twice at the right arm after a 15-min rest in the sitting position, using a standard mercury sphygmomanometer. Height and weight were measured using a stadiometer. Heavy outer garments and shoes were removed before measuring height and weight. Body Mass Index (BMI) was calculated. Waist circumference was defined at the midway level between the costal margins and the iliac crests. Hip circumference was measured at the level of the greater trochanters. A fasting blood sample was taken, all samples were promptly centrifuged, separated and analyses were carried out at the Persian Gulf Health Research Center on the day of blood collection using a Selectra 2 autoanalyzer (Vital Scientific, Spankeren, The Netherlands). Glucose was assayed by enzymatic (glucose oxidase) colorimetric method using a commercial kit (Pars Azmun Inc.; Tehran, Iran). Serum total cholesterol and HDL-cholesterol were measured using a cholesterol oxidase phenol aminoantipyrine and triglycerides using a glycerol-3 phosphate oxidase phenol aminoantipyrine enzymatic method. Serum LDL-cholesterol was calculated using the Friedwald formula; LDL-cholesterol was not calculated when triglycerides concentration was >400 mg/dl.

2.2. Definitions

The metabolic syndrome was diagnosed with the criteria indicated by the NCEP-ATP III [4]. According to these criteria, subjects with the metabolic syndrome are those with any combination of three or more of the following risk determinants: fasting plasma glucose ≥6.1 mmol/l, blood pressure ≥130/≥85 mmHg or antihypertensive treatment, plasma triglycerides ≥1.7 mmol/l, plasma HDL cholesterol <1.03 mmol/l in men and <1.29 mmol/l in women, and waist circumference >102 cm in men or >88 cm in women.

Smoking was considered to be present when the participant smoked cigarettes or used a shisha (water pipe) daily. Respondents were classified as active at the recommended level if they reported sufficient physical activity of moderate intensity (≥30 min per day ≥5 days per week) or of vigorous intensity (≥20 min per day ≥3 days per week) [29].

The aggregate number of seropositivities to *C. pneumoniae*, *H. pylori*, cytomegalovirus or herpes simplex virus type 1 was defined as pathogen burden [30].

2.3. Serology

IgG antibodies against *C. pneumoniae* were measured by a commercial test kit (DRG Instruments GmbH, Germany). The principle of the kit was based on an indirect solid-phase enzyme immunoassay with horseradish peroxidase as a marker enzyme; the positivity threshold was enzyme immunounits (EIU) >45. Sera were screened for IgG antibodies against herpes simplex virus type 1, cytomegalovirus and *H. pylori* with an ELISA (RADIM SpA, Italia), and the samples were considered positive with IgG values higher than 30 RU/ml for CMV and *H. pylori*. Samples with optical density higher than

Table 1 – Clinical characteristics and laboratory values of a random population of the northern Persian Gulf (the study population) according to the metabolic syndrome (The National Cholesterol Education Program Adult Treatment Panel III).

	Normal (n = 841)	Metabolic syndrome (n = 913)	p value
BMI, kg/m^2[a]	25.6 (5.2)	28.6 (4.9)	<0.0001
Systolic blood pressure, mmHg	116.7 (23.3)	134.7 (45.3)	<0.0001
Diastolic blood pressure, mmHg	74.8 (21.5)	85.6 (44.7)	<0.0001
Total Cholesterol, mg/dl	193.6 (45.5)	217.4 (47.0)	<0.0001
HDL-cholesterol, mg/dl	50.7 (45.5)	39.2 (26.7)	<0.0001
LDL-cholesterol, mg/dl	120.5 (58.8)	133.0 (48.5)	<0.0001
Triglyceride, mg/dl	111.4 (60.7)	225.4 (102.9)	<0.0001
Fasting blood sugar, mg/dl	82.3 (16.7)	101.3 (51.9)	<0.0001
C-reactive protein, mg/l[b]	1.4 (3.9)	2.5 (3.6)	<0.0001
Smoking, %	28.5	29.6	N.S
Physical inactivity, %	71.8	70.2	N.S
Chlamydia pneumoniae, seropositive, %	16.1	24.6	<0.0001
Helicobacter pylori seropositive, %	26.9	34.8	<0.0001
Cytomegalovirus seropositive, %	44.0	49.2	0.01
Herpes simplex type 1 seropositive, %	40.2	45.9	0.02

Values are mean (SD), except for smoking, physical inactivity and seropositivity to infectious markers.
[a] BMI indicates body mass index.
[b] Geometric mean (SD).

cut-off control were considered reactive for anti-HSV type 1 IgG antibodies.

Measurement of CRP by a high-sensitivity CRP assay, CRP HS ELISA (DRG International, Inc. USA) was done. The minimum detectable concentration of the CRP HS ELISA assay was estimated to be 0.1 mg/l. Additionally, the functional sensitivity was determined to be 0.1 mg/l (as determined with inter-assay %C.V. <20%).

2.4. Statistical methods

The significance of the difference in the results of any two groups was determined by chi-square analysis using 2×2 contingency tables for categorical variables and ANOVA for continuous variables. A two-tailed t-test was used to compare the mean values across groups.

We found that log transformation of hs-CRP gave a better fit to a Gaussian distribution. The geometic mean for hs-CRP was defined as the arithmetic mean of the log-transformed data $\pm$2SD, raised to the power of 10.

Multiple logistic regression analysis was used to ascertain the associations between log hs-CRP and the metabolic syndrome. Sex, age, smoking, physical inactivity, hypercholesterolemia and pathogen burden (4, 3, 2 pathogens versus 0–1 pathogen) were considered as covariates, and the metabolic syndrome also as the dependent variable in multiple models. We excluded from statistical analysis 187 subjects with hs-CRP concentrations $\geq$10.0 mg/l to exclude possible cases of acute infections and other occult diseases. $p < 0.05$ was considered statistically significant. Statistical analysis was performed with an IBM computer using the SPSS 9.05 statistical software package (SPSS Inc., Chicago, IL).

3. Results

We have presently analyzed a total of 1754 (49.2% males, 50.8% females) subjects for the association of the metabolic syndrome, hs-CRP and infectious burden. Of the studied subjects, 36.1% was between 25 and 34 years, 29.0% between 35 and 44 years, 21.9% between 45 and 54 years, and 12.7% between 55 and 66 years. Relevant anthropometric information including cardiovascular risk factors and biochemical information in persons with and without the metabolic syndrome are given in Table 1.

The prevalence of consumption of antihypertensive, hypolipidemic and anti-diabetic drugs were 6.5%, 3.5% and 3.8%, respectively.

A total of 913 (52.1%) of the subjects (56.30% of males and 48.0% of females; $p < 0.0001$) had the metabolic syndrome (NCEP-ATP III criteria).

The geometric mean of CRP was 1.94 mg/l (1.03 SE) in the studied population. Quartiles (Q) for the population distribution for CRP were as follows: Q1, 0.04–0.80 mg/l; Q2, 0.81–1.70 mg/l; Q3, 1.71–4.50 mg/l; and Q4, 4.51–338.00 mg/l. CRP levels were higher in women (geometric mean = 2.29 mg/l) than men (geometric mean = 1.62 mg/l), ($p < 0.0001$). The subjects with the metabolic syndrome had a higher geometric mean of CRP levels than the normal persons [2.51 (SE 1.04) versus 1.46 (1.05) mg/l, respectively; $p < 0.0001$)] (Table 1).

Age-adjusted odds ratio (95%, CI) between the metabolic syndrome and hs-CRP levels was 1.48 (1.12–1.95), $p = 0.005$ for men and 2.41 (1.85–3.14), $p < 0.0001$ for women.

The prevalence of IgG antibodies against CMV, HSV, *C. pneumoniae* and *H. pylori* were higher in subjects with the metabolic syndrome than healthy persons (Table 1). The prevalence of the number of pathogens (0–1, 2, 3, and 4) was 6.3%, 26.3%, 42.9% and 23.9%, respectively. There was an increased trend of prevalence of the metabolic syndrome with increasing number of pathogens (4.0%, 22.6%, 43.4% and 29.7% for 1, 2, 3, and 4 pathogens, respectively; p for trend < 0.0001). A linear relationship between an increase in the number of pathogens and CRP concentrations was also observed ($p = 0.003$).

The individual components of the metabolic syndrome as well as the concentration of the hs-CRP were analyzed (data

Table 2 – Multivariately adjusted odds ratios (OR) and 95% confidence intervals (CI) relating hs-CRP and the metabolic syndrome among the study population[a].

Independent variables	Two pathogen			Three pathogen			Four pathogen		
	OR	95% CI	*p* value	OR	95% CI	*p* value	OR	95% CI	*p* value
Hypercholesterolemia (≥240 vs <240 mg/dl)	0.90	0.53–1.51	0.69	1.82	1.21–2.74	0.004	1.17	0.70–1.96	0.54
log CRP, mg/l	2.06	1.32–3.21	0.001	1.75	1.26–2.42	0.001	2.12	1.46–3.08	<0.0001
Smoking (yes vs no)	0.54	0.33–0.88	0.01	0.76	0.52–1.11	0.16	0.85	0.53–1.37	0.51
Physical inactivity (yes vs no)	1.39	0.89–2.18	0.14	1.47	1.04–2.10	0.02	0.96	0.61–1.51	0.88
Sex (male vs female)	2.07	1.37–3.12	<0.0001	1.69	1.22–2.35	0.002	2.28	1.49–3.47	<0.0001
Age groups (years)[b]									
35–44	1.72	1.06–2.80	0.02	1.46	0.99–2.16	0.05	1.91	1.16–3.16	0.01
45–54	2.42	1.33–4.40	0.004	2.50	1.58–3.94	<0.0001	2.46	1.37–4.42	0.003
55–66	3.23	1.51–6.92	0.003	3.24	1.74–6.01	<0.0001	2.19	1.07–4.48	0.3
Pathogen burden[c]	1.69	1.00–2.85	0.04	1.95	1.18–3.20	0.008	3.05	1.80–5.16	<0.0001

[a] log CRP considered as a single entity, sex, age, hypercholesterolemia, smoking, physical inactivity and pathogen burden as covariates, and the metabolic syndrome (NCEP ATP-III) as the dependent variable.
[b] The risks are relative to age group 24–34.
[c] The risks are relative to 0–1 pathogen.

not shown). The concentrations of hs-CRP were significantly higher in all components of the metabolic syndrome ($p < 0.0001$). A linear relationship between an increase in the number of metabolic syndrome components and CRP concentrations was observed (Fig. 1); geometric mean hs-CRP levels for those with 1 versus 5 characteristics of the metabolic syndrome were 1.18 and 4.22 mg/l, respectively (trend, $p < 0.0001$). Similar results were obtained when subjects were classified according to number of pathogens. Geometric mean of hsCRP levels for those with 1 versus 5 characteristics of the metabolic syndrome were 1.05 and 3.34 mg/l (trend, $p = 0.006$), 1.24 and 3.09 mg/l (trend, $p < 0.0001$), 1.32 and 4.66 mg/l (trend, $p < 0.0001$), 1.13 and 4.19 mg/l (trend, $p < 0.0001$) in those with 0–1, 2, 3 and 4 pathogens, respectively.

In multiple logistic regression analysis log hs-CRP, showed a significant association with the metabolic syndrome [OR = 1.96, CI (1.59–2.43), $p < 0.0001$] after adjusting for sex, age, hypercholesterolemia, smoking and physical inactivity. Serum hs-CRP levels also showed a significant association with the metabolic syndrome [OR = 1.90, CI (1.56–2.31), $p < 0.0001$] after adjusting for age, sex and subclinical infection with CMV, HSV, *C. pneumoniae* and *H. pylori*.

In multiple logistic regression models with the metabolic syndrome as the dependent variable (Table 2), log CRP and cardiovascular risk factors as independent variables, hs-CRP showed significant associations with the metabolic syndrome after controlling for infectious burden divided into 2, 3 and 4 pathogens [OR = 2.06, CI (1.32–3.21), $p = 0.001$; OR = 1.75, CI (1.26–2.42), $p = 0.\ 001$; OR = 2.12, CI (1.46–3.08), $p < 0.0001$], respectively.

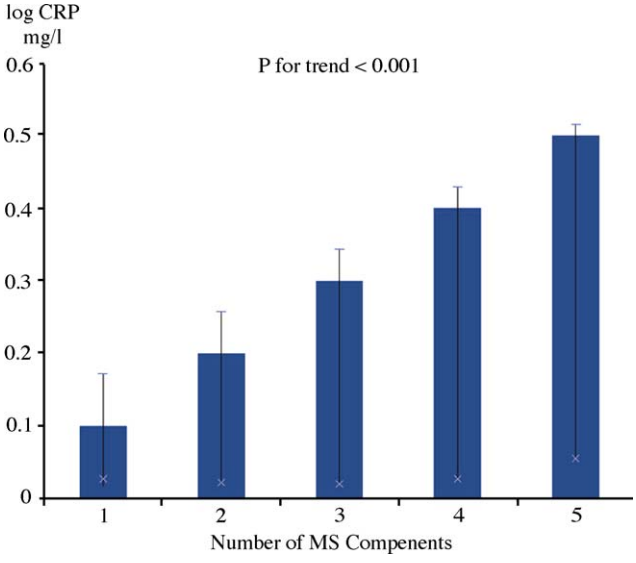

Fig. 1 – Distribution of log C-reactive protein (hs-CRP) levels according to the number of the metabolic syndrome (NCEP ATP-III) components in the study population. Data presented as means (SE).

4. Discussion

In this large-scale, population-based study, hs-CRP levels were associated with the metabolic syndrome. This association remained in the study population after adjustment for burden of viral and bacterial pathogens that had been identified as important factors influencing, inflammation, human coronary as well as carotid atherosclerosis, and the metabolic syndrome [24,24,27,31].

The concept of infectious burden is interesting; it is defined as the number of seropositivity to infectious pathogen to which an individual has been exposed [30]. The impact of viral and bacterial infectious burden on long-term prognosis in patients with coronary artery disease and essential hypertension had been shown [31,32]. There is little information about the impact of pathogen burden on the development of chronic insulin resistance or the metabolic syndrome [24–26]. These studies had controversial results about the association between pathogen burden and the metabolic syndrome or insulin resistance. A significant association between burden of infection, especially with enteroviruses and *C. pneumoniae* seropositivity, and insulin sensitivity was described in healthy middle-aged men [24]. But Howard et al. reported no relationship between pathogen burden and inflammation, and insulin

resistance, metabolic syndrome, or impaired fasting glucose in a population with high burden of subclinical infection [26].

Recently, in the first report of our population-based study, we showed that the metabolic syndrome had a significant with prior infection with HSV-1, CMV, *H. pylori* and *C. pneumoniae* [27]. Thus, it was hypothesized that these viral and bacterial pathogens induce production of proinflammatory cytokines, such as TNF-alpha and IL-6 which are leading to chronic subclinical inflammation, insulin resistance and the metabolic syndrome.

In the present study, we therefore adjusted for burden of the latter infectious agents, which could confound association of the metabolic syndrome and hs-CRP, in logistic regression models. We observed that the association between CRP and the metabolic syndrome persisted after controlling for 2, 3, and 4 numbers of organisms that had been previously associated with coronary artery disease.

The association of infectious burden and metabolic abnormalities, with the degree of inflammation was compared in 569 patients with coronary artery disease [25]. They concluded that compared with infectious burden, metabolic abnormalities had a more prominent association with the degree of inflammation, severity of coronary atherosclerosis and the major cardiovascular events [25]. Our findings are in agreement with their conclusions and suggest hs-CRP is associated with the metabolic syndrome, independent to the number of infectious pathogens which an individual has been exposed.

Multiple cross-sectional and prospective epidemiological studies showed an association between hs-CRP and the metabolic syndrome and its components [11–20]. However, the mechanisms responsible for the low-grade up-regulation of CRP production that predicts development of the metabolic abnormalities in general population are not clearly understood. It has been hypothesized that increased secretion of IL-6 and proinflammatory cytokines from expanded adipose tissue mass up-regulates the production of CRP by the liver. This in turn can induce insulin resistance and results in accentuation of other metabolic abnormalities that constitute the metabolic syndrome [15,33].

Genetics also influences relationship of CRP, insulin resistance and the metabolic syndrome. Substantial genetic effects in CRP variation are present outside the CRP gene itself. A genome-wide association study among 6345 apparently healthy women in the Women's Genome Health Study revealed that most of the common genetic polymorphism that contributes to CRP level was closely related to genetic pathways known to have an impact on metabolic syndrome, insulin resistance, beta cell function, weight homeostasis, and/or premature atherosclerosis [34]. These genetic findings linking chronic, low-grade inflammation to loci known functionally to relate to metabolic abnormalities to be of considerable interest given epidemiologic data linking hs-CRP levels to the metabolic syndrome and its components. These genetic data support a potential causal role for CRP itself.

Our study confirmed that levels of hs-CRP were positively correlated with the number of components of the metabolic syndrome according to NCEP definitions.

Several studies have reported a relationship between components of the metabolic syndrome, according to the ATP III definition, and hs-CRP [16,17,20,35,36].

Intravascular kinetics of CRP, using stable isotopes, revealed that the CRP production rate, as the main determinant of CRP concentrations, had significant association with features of the metabolic syndrome as well as with adipose tissue-derived cytokines such as IL-6 and adiponectin [37]. In Finnish population-based study, decreased levels of adiponectin and increased levels of hs-CRP and IL-Ira were tightly associated with the components of the metabolic syndrome [36]. These data could explain our finding of a gradual increase in log CRP levels with increasing numbers of the metabolic syndrome components.

Fernandez-Real et al. suggested that inflammation is behind the link between pathogen burden and insulin resistance because significant relationship between the number of infectious pathogens and insulin sensitivity did not persist after controlling for CRP [24]. But significant association of pathogen burden and the metabolic syndrome persisted in our regression models when CRP levels were simultaneously entered. This finding suggests that inflammation does not significantly influence the relationship between the metabolic syndrome and pathogen burden and both inflammation and pathogen burden are independently associated with the metabolic syndrome.

In the present study, women had higher hs-CRP levels than men. The metabolic syndrome also showed a higher age-adjusted association with elevated hs-CRP levels in women than men. However, the prevalence of the metabolic syndrome was significantly higher in men than in women. This discrepancy shows that the relationship of hs-CRP and the metabolic syndrome is not a simple cause and effect and multiple factors should be considered in a complex system to explain the ethiopathogenesis of the metabolic syndrome.

Blood levels of CRP and IL-6 are also associated with higher risk of Alzheimer disease and cognitive decline during aging [38]. Recent evidences also suggest that the metabolic syndrome is a risk factor for accelerated cognitive aging, especially among those with high levels of inflammation [39,40]. To reduce the potential adverse effects of the inflammation that accompanies the metabolic syndrome and the cognitive decline, those with this syndrome should avoid excessive energy intake, and increase their daily physical activities.

We acknowledge study limitations. In the present study we used NCEP-ATP III definition for the metabolic syndrome. Although this definition is most often used, other definitions for the metabolic syndrome do exist. Another limitation of our study includes the lack of measurement of insulin resistance from fasting glucose and insulin concentrations using the HOMA method. Another limitation is that we used a single CRP measurement that may not accurately reflect long-term inflammation status. We conducted our study in a large random population and used seropositivity as a marker for infections; however, it has the advantage of clinical applicability, but the assessment of infection status based on serology without further clinical or laboratory characterization is subject to diagnostic inaccuracies, especially if seropositivity is common because of the widespread distribution of the incriminated microorganism. In our study, the presence of seropositivity to other confounding viral or bacterial pathogens cannot be ruled out.

The present cross-sectional study does not allow for inferring causality from the results. Future research should include longitudinal studies of the metabolic syndrome, proinflammatory biomarkers and a comprehensive survey for chronic viral and bacterial infections to determine temporal sequence of any relationship.

In conclusion, in a large representative sample of Iranian population, we showed a strong association between inflammation and the metabolic syndrome, independent to burden of common viral and bacterial infections pathogens that had been previously associated with human coronary as well as carotid atherosclerosis. Although it is difficult to conclude if low-grade inflammation induces insulin resistance and the metabolic syndrome or is a consequence, strong association of hs-CRP levels and the metabolic syndrome independently to chronic infections promises to be exciting and groundbreaking. The effective administration of anti-nflammatory agents, in the treatment of insulin resistance and atherosclerosis is only the beginning of a new approach in the management of the metabolic syndrome.

Conflict of interest

The authors declare that they have no conflict of interest.

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